IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent Application of:		**Customer No.:**	**23448**
Applicant:	**Von Knebel-Doeberitz, et al.**	**Docket No.:**	**4121-121**
Serial No.:	**09/719,336**	**Examiner:**	**C. Qian**
Date Filed:	**March 22, 2001**	**Art Group:**	**1633**
Title:	**USE OF ADENO-ASSOCIATED VIRUSES FOR DECREASING THE RADIOTHERAPY-INDUCED OR CHEMOTHERAPY-INDUCED RESISTANCE IN CANCER PATIENTS**	**Confirmation No.**	**7154**

23448
PATENT TRADEMARK OFFICE

EXPRESS MAIL CERTIFICATE

I hereby certify that I am mailing the attached documents to the Commissioner for Patents on the date specified below, in an Express Mail envelope addressed to the Commissioner for Patents, Box RCE, Washington, DC 20231, and Express Mailed under the provisions of 37 CFR 1.10.

Lauren Ashe

Lauren Ashe

December 13, 2002
Date of Mailing

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PRELIMINARY AMENDMENT FILED WITH A REQUEST FOR CONTINUED EXAMINATION IN U.S. PATENT APPLICATION NO. . 09/719,336, DECLARATION OF INVENTORS AND PETITION UNDER 37 CFR §1.36 FOR A THREE MONTH EXTENSION OF TIME

BOX RCE
Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the September 13, 2002 Advisory Action in the above-identified application, applicants submit herewith a Declaration by Dr. Magnus Von-Knebel-Doeberitz that provides further evidence that the presently claimed invention provides for effective treatment of cancer.

During a recent telephonic conversation with Examiner Qian, the undersigned attorney was informed that further tests results would be required to show the efficacy of the claimed invention in an immunocompetent animal model.

In the enclosed Declaration (Appendix A) Dr. Von-Knebel-Doeberitz describes tests results clearly demonstrating that AAV infection prior to treatment with 5-FU compared to 5-FU treatment alone significantly reduced the viability of pancreatic cancer cells *in vitro* and reduced tumor growth in **immunocompetent Lewis rats** challenged with syngeneic pancreatic cancer cells. Furthermore, chemotherapy-related toxic side effects, such as thrombocytopenia, neutropenia, loss of weight and pain, were significantly reduced in the immunocompetent animals treated with concomitant AAV infection.

Dr. Von-Knebel-Doeberitz further testified that the use of AAV-2-mediated sensitization of tumor cells to cytotoxic drugs and reduced chemotherapy-related toxic side effects. As shown in Table 2 of the Declaration, the combination of intratumoral AAV-2 infection of implanted pancreatic DSL6A tumors with additional systemic 5-FU chemotherapy resulted in significant retardation of tumor growth and prolonged survival of the immunocompetent Lewis rats. Further, the combined effects clearly exceeded those achieved by administration of either agent alone.

It was further shown by the tests results set forth in the Declaration that concomitant AAV-2 infection, provided a striking improvement of the clinical benefit response when compared to untreated or 5-FU monotherapy-treated animals. In AAV-infected Lewis rats, body weight, hemoglobin and number of white blood cells were similar to those of healthy rats. The most remarkable change of response to high-dose 5-FU therapy when combined with additional intratumoral AAV infection was a rise in the number of monocytes from a mean of 2 cells/µl in 5-FU-treated rats to 1,002/µl, which represents a 4- to 5-fold

increase compared to the value in healthy rats (220 cells/μl). In addition, in all AAV-2-treated animals, the number of neutrophil cells was markedly increased.

These results clearly showed the potential use of AAV-2-mediated sensitization of tumor cells to cytotoxic drugs and that the combination of chemotherapy with AAV-2 infection led to a more pronounced decline of tumor volume compared with animals that received only chemotherapy, indicating a sensitization of drug-treated tumor cells. These results showed that applicants' claimed invention is effective as a cancer treatment in cell, and two different animal, and as such, applicants have clearly shown the efficacy of the claimed treatment method. Accordingly, applicants respectfully request that all rejections be withdrawn.

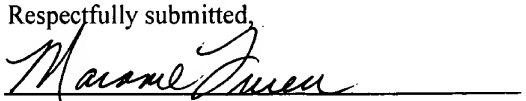
Petition for Extension of Time/Fees Payable

The applicants hereby petition for a three (3) month extension of time, extending the deadline for responding to the July 2, 2002 Office Action from October 2, 2002 to January 2, 2003. The entry of this petition results in a petition fee of $460.00. A check in the amount of $830.00 is submitted herewith which includes the petition fee for a three month extension and the filing fee for a Request for Continued Examination. The U.S. Patent and Trademark Office is hereby authorized to charge any additional amount necessary to the entry of this amendment, and to credit any excess payment, to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

CONCLUSION

Pending claims 1-15 meet all requirements of patentability and are in condition for allowance. If any issues remain outstanding, incident to allowance of the application, the Examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss their resolution, in order that this application may be passed to issue at an early date.

Respectfully submitted,



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